
بسم الله الرحمن الرحيم

H1N1 and kidney

By

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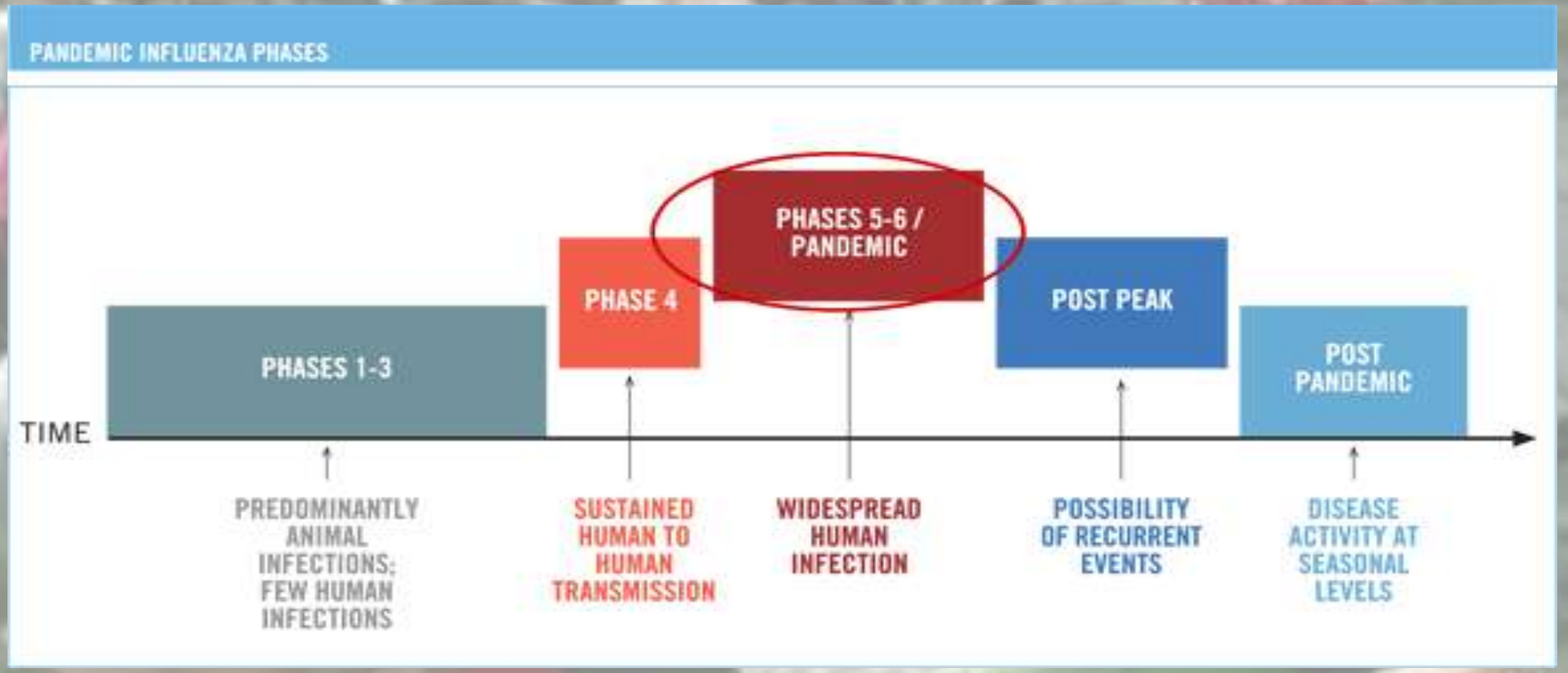
(NEPHROLOGY)

In late March and early April 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico, with subsequent cases observed in many other countries, including Egypt.

- In June 2009, the World Health Organization (WHO) raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission.



- The United States (CDC) estimated that between April 2009 and April 2010, about 61 million cases of pandemic H1N1 influenza occurred in USA, with about 12,470 deaths
- The pandemic was declared to be over in August 2010.

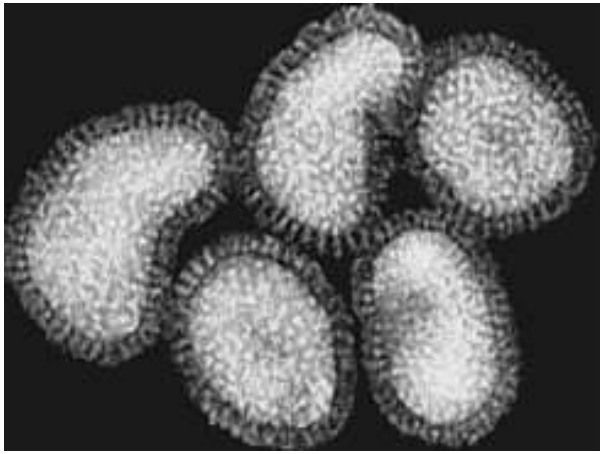
However, H1N1 flu is still making people sick, even killing some patients in random areas of the world, and experts expect it to do so for years with expected waves of epidemics.

Influenza Pandemics of the past years

Year of Origin	Sub-Type in Circulation
1890	H2N8
1900	H3N8
1918	H1N1 (Spanish Flu)
1957	H2N2 (Asian Flu)
1968	H3N2 (Hong Kong Flu)
1977	HIN1 (Russian Flu)

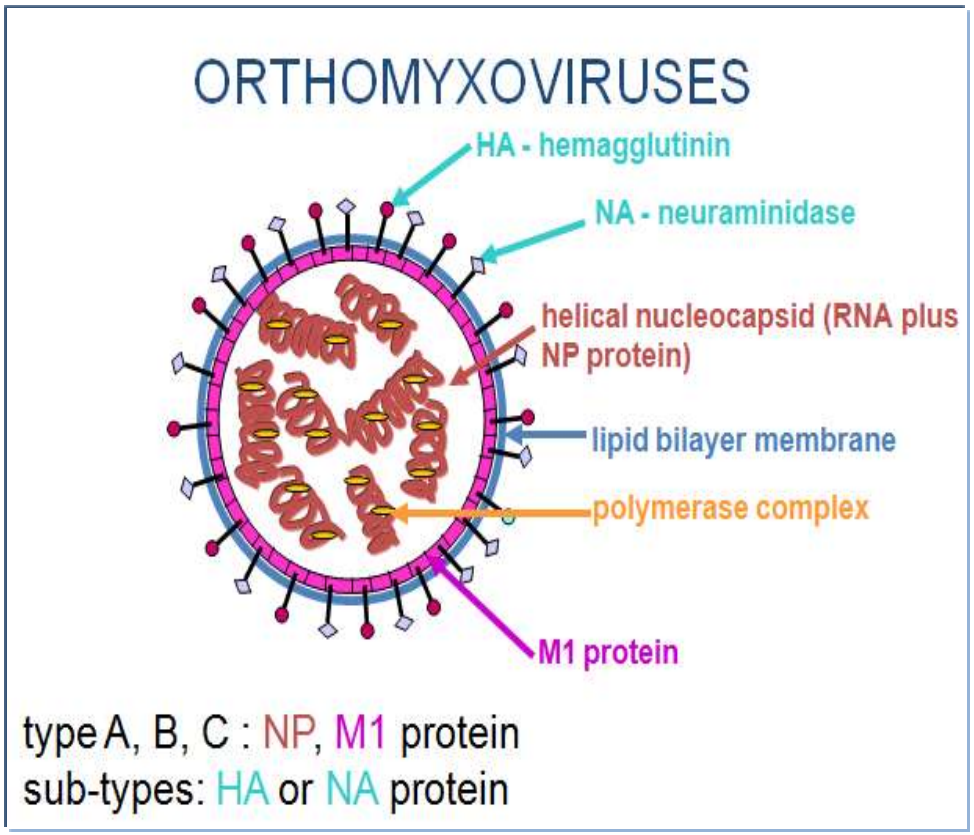

The 1918 “Spanish Flu” pandemic (H1N1) killed about 40-50 million people worldwide in less than one year.
The total military deaths in WW1 were 8.3 million over 4 years

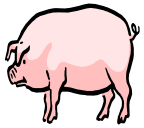
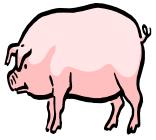
Influenza Virus



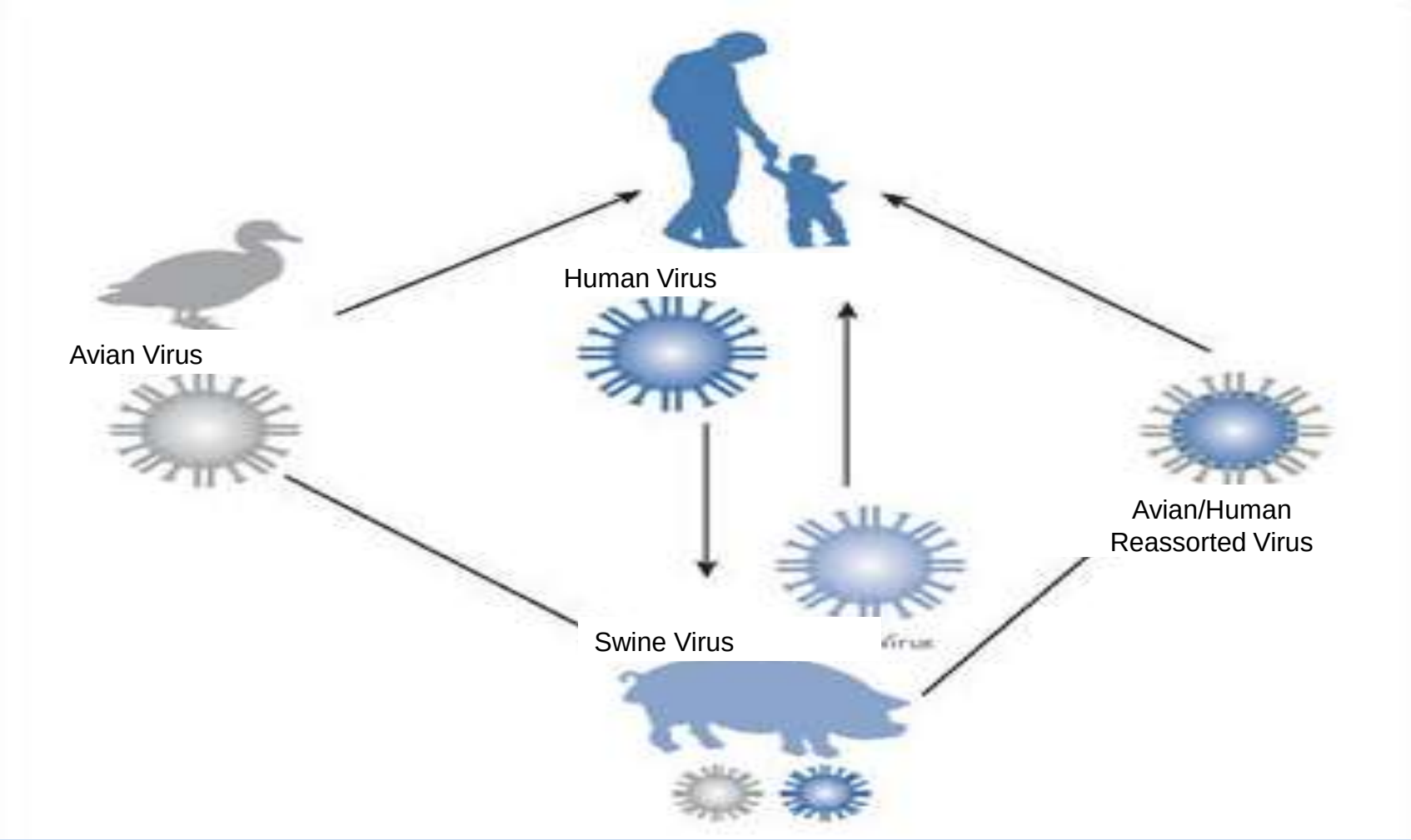
- Enveloped RNA virus
- Viral family: Orthomyxoviridae

- Three types based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens.
  - A, B, C
- Surface antigens
  - H (haemaglutinin)
  - N (neuraminidase)

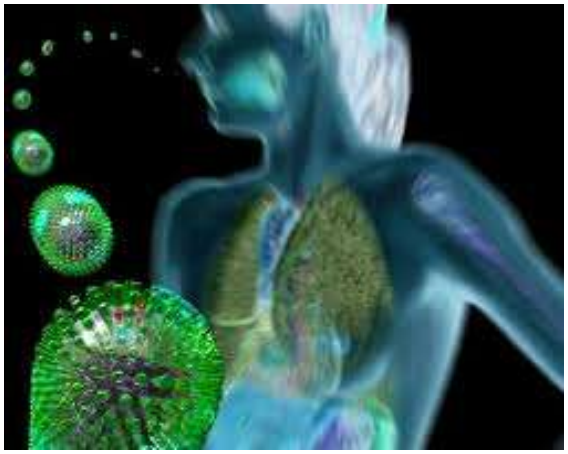


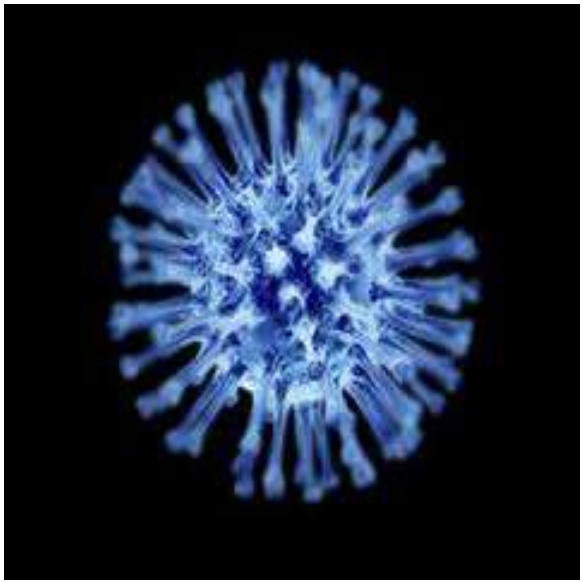
Haemagglutinin subtype					Neuraminidase subtype				
									
H1					N1				
H2					N2				
H3					N3				
H4					N4				
H5					N5				
H6					N6				
H7					N7				
H8					N8				
H9					N9				
H10									
H11									
H12									
H13									
H14									
H15									
H16									

The emergence of a novel influenza virus subtype that can infect the human population requires **antigenic shift**.



How does H1N1 Influenza spread?





- Primarily through respiratory droplets
  - Coughing
  - Sneezing
  - Touching respiratory droplets on yourself, another person, or an object, then touching mucus membranes (e.g., mouth, nose, eyes) without washing hands

Population *At Risk* for a Severe H1N1 infection are:

- Pregnant women
- Children 0 – 5 years of age
- Patients with chronic medical conditions
  - Pulmonary asthma, cystic fibrosis, COPD
  - Immune compromised
  - Medically fragile

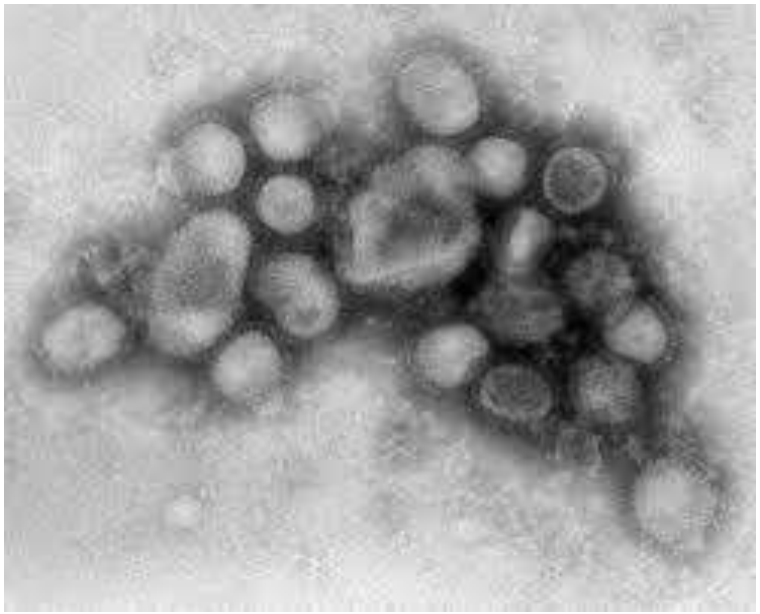
H1N1 Hospitalizations Reported to the CDC: Underlying Medical Conditions, as of June 19, 2009 (N=268)

- Asthma H1N1 Hospitalized, 32%
- COPD H1N1 Hospitalized, 32%
- Diabetes, H1N1 Hospitalized, 15%
- Chronic CVD, H1N1 Hospitalized 14%
- Immunocompromised, H1N1 Hospitalized, 13%
- Current Smoker, H1N1 Hospitalized, 10%
- Chronic Renal Dis III/IV, H1N1 Hospitalized, 9%
- Obesity, H1N1 Hospitalized, 8%
- Neurocognitive Dis. H1N1 Hospitalized, 7%
- Pregnant, H1N1 Hospitalized, 6%
- Seizure, H1N1 Hospitalized, 6%
- Cancer, H1N1 Hospitalized, 3%

Incubation and Communicability

Incubation Period

- 1 – 3 days



Contagious Period

- 1 day before symptoms, 3-5 days after onset of symptoms (up to 7 days in young children)

Clinical diagnosis: acute onset fever and cough can be predictive during epidemics.

Several rapid antigen and immunofluorescent antibody tests are available for the diagnosis of influenza virus infection. However, the sensitivity of these tests varies widely, and they do not differentiate between pandemic and seasonal strains of H1N1 influenza A.

Confirmation of pandemic H1N1 influenza A infection could only be made by real-time reverse-transcriptase **(rRT)-PCR or culture** from upper respiratory tract samples.

ILLNESS SEVERITY IN (H1N1)

Mild or uncomplicated illness : characterized by fever, cough, sore throat, rhinorrhea, muscle pain, headache, chills, malaise, and sometimes diarrhea and vomiting.

Progressive illness: characterized by typical symptoms plus chest pain, poor oxygenation, cardiopulmonary insufficiency, CNS impairment, severe dehydration, or exacerbations of chronic conditions.

Severe or complicated illness: characterized by:

- signs of lower respiratory tract disease (eg, hypoxia requiring supplemental oxygen, mechanical ventilation, or abnormal chest radiograph).
- CNS findings (encephalitis, encephalopathy).
- complications of hypotension (shock, organ failure).
- myocarditis or rhabdomyolysis, or invasive secondary bacterial infection.

ASYMPTOMATIC INFECTION

There is a study that found that about 9% of H1N1 infection is asymptomatic.

DOI: **http://dx.doi.org/10.4081/nr.2011.e8**

Atypical presentation of influenza A/H1N1 in a chronic kidney disease patient

Vivek B. Kute, Hargovind L. Trivedi, Pankaj R. Shah, Aruna V. Vanikar, Manoj R. Gumber

Uremia-induced immune dysfunction .

Antiviral therapy

- Antiviral therapy was recommended for individuals with suspected or confirmed H1N1 infection with severe illness with risk factors for complications (eg, pregnancy, age <5 or >65 years, severe immunocompromise).
- A neuraminidase inhibitor (oral oseltamivir or orally inhaled zanamivir) was recommended.
- Peramivir, is an investigational iv

Vaccination

- By monovalent vaccine, since the trivalent (seasonal) influenza vaccine did not contain antigens from this strain.

Influenza A/H1N1 Vaccine in Patients Treated by Kidney Transplant or Dialysis: A Cohort Study

Nilufer E. Broeders, Anneleen Hombrouck,† Anne Lemy, Karl Martin Wissing,‡ Judith Racapé,* Karine Gastaldello,* Annick Massart,* Steven Van Gucht,† Laura Weichselbaum,* Aurelie De Mul,* Bernard Brochier,† Isabelle Thomas,† and Daniel Abramowicz**

Conclusions The influenza A/H1N1-adjuvanted vaccine is of limited efficacy but is safe in renal disease populations. The humoral response is lower in transplanted *versus* hemodialyzed patients. Further studies are needed to improve the efficacy of vaccination in those populations.

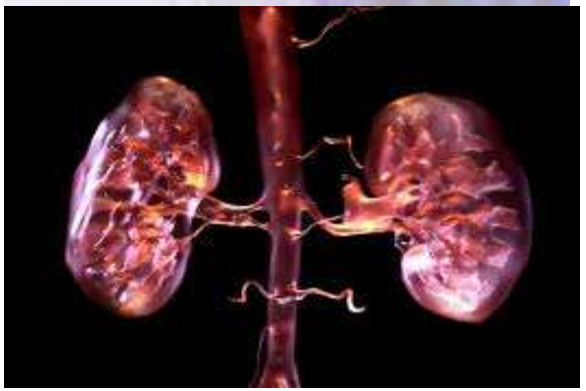
Clin J Am Soc Nephrol 6: 2573–2578, 2011. doi: 10.2215/CJN.04670511

COMPLICATIONS AND ADMISSION CRITERIA

Complications include the following (this section has been adapted from the Centers for Infectious Disease Research and Policy [41]):

- Diffuse viral pneumonitis (can be associated with severe hypoxia and acute respiratory distress syndrome [ARDS])
- Shock and renal failure among some patients with ARDS
- Prolonged exacerbation of chronic obstructive pulmonary disease (COPD)
- Secondary bacterial pneumonia
- Neurologic manifestations (eg, altered mental status, seizures, encephalopathy, encephalitis)
- Myocarditis
- Dehydration
- Death

The World Health Organization (WHO) warned physicians that patients with H1N1 virus infection might develop renal impairment ranging from just mild disease to the need for renal replacement therapy



Renal complications of influenza A virus infections

- Acute kidney injury (AKI) in critically ill patients.
- Rhabdomyolysis.
- Hemolytic uremic syndrome (HUS) following secondary *Streptococcus pneumoniae infection* in patients with genetic complement dysregulation.
- Acute glomerulonephritis (AGN).
- Disseminated intravascular coagulation (DIC).
- Goodpasture's syndrome.
- And acute tubulointerstitial nephritis (TIN).

Acute kidney injury (AKI) in critically ill patients with H1N1

- AKI is more frequent in patients with severe H1N1, with an incidence of around 50-60%.

- Many patients develop a severe form of AKF, requiring dialysis in up to a quarter of the patients, and is associated with an increased risk of mortality.

- Among the survivors, there are case reports of patients who did not fully recover their kidney function, months after hospital discharge.

ORIGINAL ARTICLE

Anaesth Pain & Intensive Care 2010;14(1):13-16.)

Acute kidney injury in patients with H1N1 admitted to ICU: Incidence, patient and renal outcomes. A multi-center perspective

Samra Abouchacra*, Ahmed Chaaban*, Nicole Gebran*, Mohamad Hassan, Abed Paul***, Hassan Al Eid***, Mohamad Gilali***, Said Abuhasna***

Tawam Hospital, United Arab Emirates
Sheikh Khalifa Medical City, United Arab Emirates
King Faisal Specialist Hospital and Research Center, Saudi Arabia

Objectives: To evaluate the rate of AKI in patients admitted to ICU with H1N1 and their outcome.

Conclusion: Our results indicate that varying degrees of AKI occur in more than half of H1N1 patients admitted to ICU. This represents a serious complication predicting worsened outcome. Though the mortality rate was high, the majority of patients recovered partially or completely with early aggressive treatment.

Patient outcome (n)	
? Complete recovery	5
? Partial recovery	3
? Dialysis dependent	1
? Death	4

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CASE REPORT

Acute kidney Injury in critically ill patients with H1N1 Infection

G.K. Manu , G. Lakshminarayana A.Mathew, R. Rajesh, G.Kurian, V.N.Unni

CONCLUSION

Primary viral pneumonia is the main cause of ICU admission in (H1N1) infected patients, developing severe respiratory failure and it is associated with a relatively high mortality. In the critically ill due to H1N1, renal insufficiency is one of the complications. In our study, Acute Kidney Injury was noted in 18% and dialysis requiring renal failure in 3% of subjects. Mortality was associated with multiple organ failure, sepsis, shock, prolonged ventilator requirement, ICU stay and acute kidney injury.

Martin-Loeches *et al. Critical Care* 2011, **15**:R66
http://ccforum.com/content/15/1/R66

CRITICAL CARE

RESEARCH Open Access

Acute kidney injury in critical ill patients affected by influenza A (H1N1) virus infection

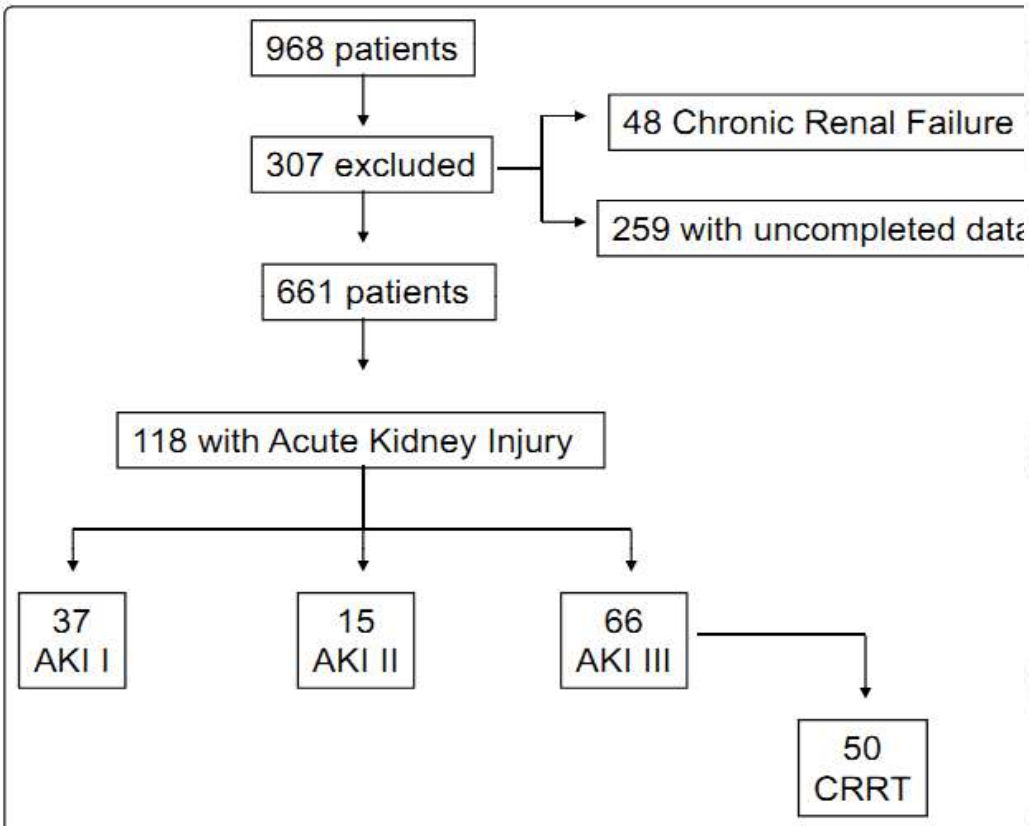

Figure 1 Flowchart of critically ill patients enrolled in the study with 2009 pandemic influenza A (H1N1) virus infection. AKI, ac
kidney injury; CRRT, continuous renal replacement therapy.

Variables	Non AKI *n* = 543	AKI *n* = 118	*P* value
ICU death, *n* (%)	72 (13.3%)	52 (44.1%)	<0.001
MV days[b]			
Mean (±SD)	8.4 (11.5)	13.6 (15.2)	<0.001
Median (IQR)	4 (0 to 12)	10 (3.75 to 21.5)	
LOS ICU[c]			
Mean (±SD)	12.6 (13)	19.4 (16.5)	<0.001
Median (IQR)	8 (4 to 17)	13 (7 to 30)	
Hospital LOS[c]			
Mean (±SD)	20.5 (16.8)	30.3 (19.9)	<0.001
Hospital median (IQR)	15 (9 to 27)	26.5 (13.75 to 44.25)	

BMC Nephrol. 2013; 14: 123.
Published online Jun 13, 2013. doi: 10.1186/1471-2369-14-123
PMCID: PMC3694036

Acute kidney injury among critically ill patients with pandemic H1N1 influenza A in Canada: cohort study

Sean M Bagshaw,[1] Manish M Sood,[2] Jennifer Long,[3] Robert A Fowler,[4,5] and Neill KJ Adhikari[corresponding author4], Canadian Critical Care Trials Group H1N1 Collaborative
Author information ▶ Article notes ▶ Copyright and License information ▶

- The objective was to describe the incidence of AKI in these patients and risk factors for AKI, renal replacement therapy (RRT), and mortality.

Results

- AKI was common, complicating the course of 60.9% of patients.
- 24.9% of those with AKI, received RRT.
- pH1N1 patients whose course was complicated by AKI received greater intensity (i.e. invasive mechanical ventilation, vasoactive support, and RRT) and duration of support in ICU, with comparable length of hospital stay and mortality.

Acute kidney injury (AKI) in critically ill patients with H1N1

- Underlying risk factors for developing AKI in H1N1 infected patients include :older age, diabetes mellitus, obesity, pregnancy, history of asthma, and chronic kidney disease.

- Histologic examination of the kidneys from patients with A(H1N1)pdm09 infection who died include acute tubular necrosis (ATN), myoglobin pigment, and DIC. A(H1N1)pdm09 is present in the kidneys of some patients.

Mechanism of renal involvement in H1N1

1) The renal affection is part of **a systemic inflammatory response syndrome** (SIRS) of viral origin named "viral sepsis," with multi-organ failure. Renal involvement during sepsis is due to cytokines and endopeptide-induced renal hypoperfusion.
2) A possible mechanism of renal involvement is **ischemia** secondary to sustained and severe hypoxemia resulting from lung affection.

- The proposed influence of the acute lung injury on renal function may be related to **mechanical ventilation-induced renal hypoperfusion**.
- Additionally, the diseased lung could express large quantities of **cytokines**, including interleukin-6 and tumor necrosis factor-α.

Mechanism of renal involvement in H1N1

A likely explanation for a possible pre-renal etiology of AKI in H1N1 infection in intensive care is the incorrect estimate of intravascular volume adequacy, as a result of pulmonary edema - characteristic of acute lung injury caused by the H1N1 virus. This aspect may have hindered interpretation of the need for adequate fluid replacement and correction of intravascular space depletion.

Another possibility to explain this etiology is that a mechanism similar to that of sepsis, wherein the cytokine released by the inflammatory process would cause vasodilation, resulting in a redistribution of blood flow and consequent low kidney input.

Mechanism of renal involvement in H1N1

3) **Glomerular microthrombosis** due to DIC, direct viral injury to the kidney, and an altered immune system with systemic mononuclear cell activation following influenza A virus infections.

4) AKI may be mediated by **antibodies or complement**, but no study could detect an immune deposits upon immunofluorescence signals.

Mechanism of renal involvement in H1N1

5) Rhabdomyolysis is the most frequently reported cause of seasonal influenza associated renal damage.

6) Recent studies have reported the virus in kidney cells and in urine samples from patients infected with H1N1. Although a direct **cytopathic** influenza virus-associated renal injury has not been reported yet, some authors suggest it may be a cause of AKI. This mechanism of renal injury seems to be highly improbable because of the transient viremia and the mild extra-pulmonary tissue damage.]

Mechanism of renal involvement in H1N1

Some authors suggest a **multifactorial mechanism**: a combination of hypoperfusion, renal vasoconstriction and rhabdomyolysis in the context of a severe systemic inflammatory response syndrome (SIRS).

Acute Kidney Injury in patients infected by H1N1 - clinical histological correlation in a series of cases

Submitted on: 10/31/2012.
Approved on: 05/14/2013.

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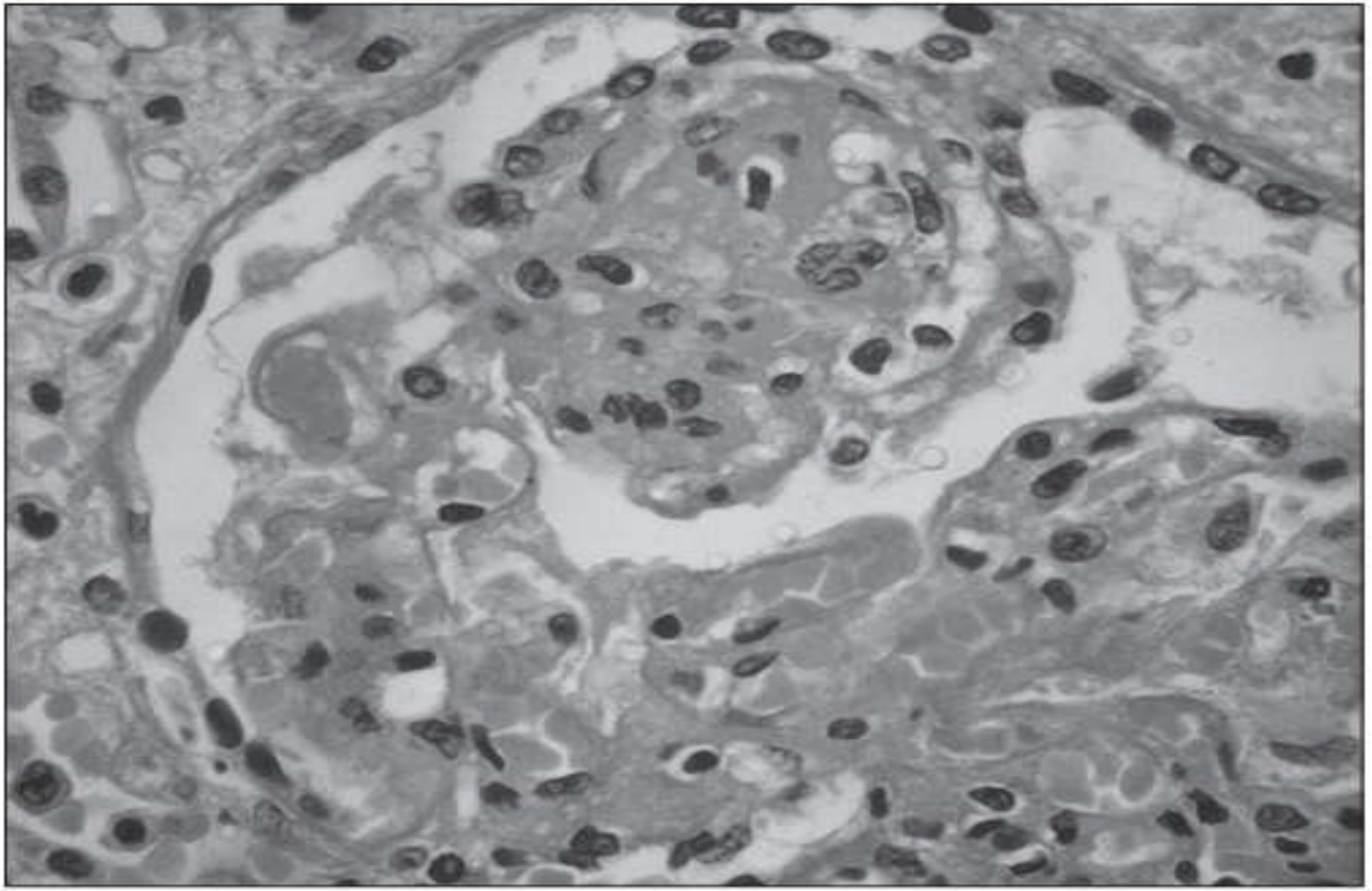
DOI: 10.5935/0101-2800.20130030

remain scarce. **Objective:** To describe the kidney histopathological findings of 6 patients with H1N1 who developed AKI and underwent kidney biopsy, correlating them with clinical features. **Methods:** We studied

Conclusion: In this study, varying degrees of vacuolar degenerative tubular changes were present in all patients, but there were no signs of acute tubular necrosis. It seems that in the present study a prerenal cause of acute renal failure was the main involved mechanim to explain the cause of renal failure in these patients.

Figure 3. Kidney sample from case #5, PAS with dig 400x: proximal tubules with vacuolar degenerative alterations.



Rhabdomyolysis in H1N1

- Recent reports showed that >40% of pandemic influenza A (H1N1/09) admissions had abnormal muscle enzyme values, implying that pandemic H1N1 virus might cause muscle damage or inflammation.

The mechanisms of rhabdomyolysis in H1N1 is unclear. But muscle damage due to direct viral invasion or induction by an immune-mediated action, have been proposed.

Acute renal failure is the most common among rhabdomyolysis patients and has been reported in about 50% of patients.

The mechanisms of renal damage in rhabdomyolysis include:

- tubular obstruction,
- The toxic effect of free chelatable iron on tubules,
- Vasoconstriction.
- Hypovolaemia or dehydration
- And aciduria (urine pH <6.5)

therefore, early and aggressive fluid repletion and bicarbonate therapy, if necessary, are the standard treatment to prevent acute renal failure.

Pediatric Infectious Disease Journal:
December 2009 - Volume 28 - Issue 12 - pp 1138-1139
doi: 10.1097/INF.0b013e3181c03cf2
Brief Reports

Melting Muscles: Novel H1n1 Influenza A Associated Rhabdomyolysis

D'Silva, Dimple MB BS*; Hewagama, Saliya MB BS†; Doherty, Richard MB BS, FRACP*‡; Korman, Tony M. MB BS, FRACP, FRCPA†§; Buttery, Jim MB BS, FRACP, MSc*‡¶

Abstract

We report the first case of myositis and rhabdomyolysis after infection with novel influenza A (H1N1/09) virus. The case demonstrates the novel virus' capacity for causing significant disease. Myositis and the possibility of rhabdomyolysis should be considered in any individual presenting with influenza-like symptoms in which severe myalgia or muscle weakness is apparent. It is likely that we will see severe clinical manifestations of infection with this novel influenza virus in the coming respiratory virus season.

內科學誌 2011：22：138-141

Influenza A(H1N1) Infection with Rhabdomyolysis and Acute Renal Failure-A Case Report

His-Pin Chen, Wei-Tung Lin, Ming-Fong Tsai, Chen-Yin Chen, and Tsung-Chang Tsai

Division of Nephrology, Department of Medicine, Antai Tian-Sheng Memorial Hospital

CONCLUSION

- It is important to monitor the kidney function of the severely ill H1N1 patients, instituting therapeutic measures of renal protection.
- There is a need for better understanding the mechanisms involved in the pathogenesis of acute kidney dysfunction that affects these patients.
- Finally, as with other patients who survive the AKI, attention should be paid to long-term monitoring of renal function in these patients.

THANK YOU